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## Metformin suppresses cisplatin resistance by down regulating Rad51 expression in triple-negative breast cancer cells

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**T**riple-Negative Breast Cancer (TNBC) is characterized by tumors that do not express the estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes. Since TNBC does not respond to endocrine therapy, this type of cancer presents an important clinical challenge. Although cisplatin is effective against TNBC, its use is limited due to the development of drug resistance. We found that metformin suppressed cisplatin resistance by downregulating Rad51, a DNA homologous recombinase. Metformin suppressed cisplatin-mediated Rad51 upregulation via regulating the protein stability and ubiquitination of Rad51. In addition, cisplatin increased phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2). Inhibition of ERK1/2 blocked cisplatin-mediated expression of Rad51. Metformin suppressed cisplatin-mediated ERK phosphorylation, indicating that metformin regulates Rad51 by suppressing cisplatin-mediated ERK activation. Moreover, metformin increased cisplatin-induced phosphorylation of  $\gamma$ -H2AX, a hallmark of DNA double-stranded breaks, suggesting that metformin enhances sensitivity to cisplatin by inducing DNA double-stranded breaks. Overexpression of Rad51 blocked the inhibition of metformin-mediated cell invasiveness, while Rad51 knockdown enhanced cisplatin-induced invasion and migration of breast cancer cells. Collectively, these results suggest that metformin prevents cisplatin resistance by regulating Rad51 expression.

### Biography

Jeongok Lee has completed her PhD at the age of 35 years from Korea University and postdoctoral studies from Korea University School of Medicine. She is the researcher in Korea University. She has published more than 10 papers in reputed journals.

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